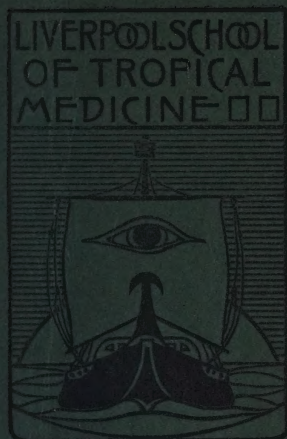


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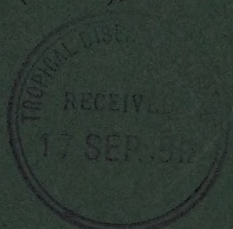
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Edited by
RONALD ROSS
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with

J. W. W. STEPHENS
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ANTON BREINL
H. B. FANTHAM

II. The Destruction of Crescents : Conclusions regarding the Prevention of Malaria by the Administration of Quinine

DAVID THOMSON, M.B., CH.B. (EDIN.),
D.P.H. (CANTAB.)



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II. THE DESTRUCTION OF CRESCENTS: CONCLUSIONS REGARDING THE PRE- VENTION OF MALARIA BY THE ADMINISTRATION OF QUININE

BY

DAVID THOMSON, M.B., CH.B. (EDIN.), D.P.H. (CANTAB.)

(Received for publication 22 May, 1912)

(A) THE DESTRUCTION OF CRESCENTS

I am still able to adhere to my previous statement that quinine in doses of twenty to thirty grains daily will reduce the crescents to numbers below one per c.mm. within a period of three weeks (Thomson, 1911). One may find a case in which they are not reduced to this negligible quantity in three weeks (Ross and Thomson, 1912), but this is altogether an exception, and indeed in the majority of cases the crescents usually disappear altogether before this three weeks' treatment is over. It was pointed out that the quinine did not destroy the crescents directly, but only indirectly by destroying the source of supply, viz., the asexual parasites. It was also stated that methylene blue, in doses of twelve grains daily, appeared to have some direct destructive action upon the crescents, but I now feel inclined to withdraw this latter statement, as further experiments have shown that the crescents under this latter treatment do not always disappear any more quickly than with quinine, and so probably the methylene blue acts only indirectly also, by destroying the asexual source of supply.

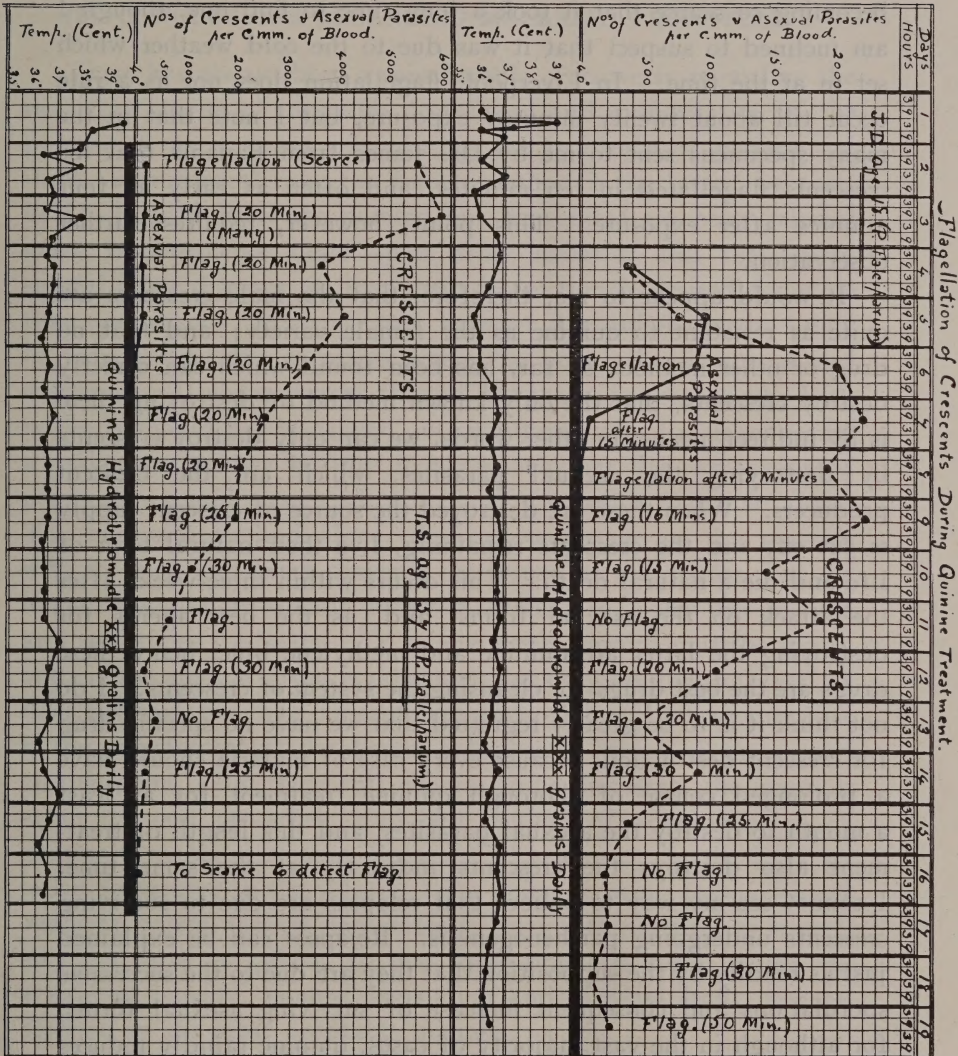
It has been stated that picric acid, in doses of six grains daily, causes crescents to disappear (Surveyor, 1910). I have unfortunately not been able to confirm its efficiency in this respect, as on five different occasions I tried this treatment, but was unable to note that it had any appreciable destructive power either upon the asexual parasites or on the crescents. On two of these occasions the picric acid was given by mouth in doses of three grains twice daily; in the remaining three, picrate of ammonia was given in similar doses.

On one occasion I tested the effect of Soamine injections, and found no reduction in the number of crescents, and there was a true fever relapse during the treatment, so that its effect on the asexual parasites could not compare with that of quinine. Again, the effect of X-Rays was tested, a patient receiving fifteen minutes' exposure over the spleen, but no reduction of crescents resulted. Also many observers have noted that '606' has little or no destructive effect on crescents. It would appear, therefore, that so far no drug or other means has been found which will directly destroy them.

Professor M. Hartmann (1911) thinks it would be possible to induce parthenogenesis in crescents, artificially, thereby transforming them into asexual parasites, which could then be destroyed by quinine. This, however, is a very theoretical statement, and even though it could be carried into practice, I think it would be a very bad method of crescent destruction, and one which might be followed by another crop of crescents about ten days after the induced parthenogenesis.

Ziemann (1906) discusses the destruction of crescents, and thinks that the macrogametes are more resistant to quinine than the microgametes, so that after some days of quinine treatment only macrogametes remain, and that these resistant macrogametes by parthenogenesis give rise to relapses. This again, however, is a more or less theoretical discussion, and lacks proof by practical experiment. Sir Ronald Ross suggested that I should try to throw more light on this point, and in consequence I made very careful observations on two cases with numerous crescents, during continuous administration of quinine, thirty grains daily. The results are shown graphically on Chart 3, which proves that during quinine treatment, so long as crescents could be found in the peripheral blood, flagellating forms could also be found. Each day a droplet of blood was placed on a glass slide, and after breathing on the slide, a cover-glass was superimposed and the film carefully searched for flagellating forms. I was able to get active flagellating forms onwards till the crescents became too few in number to be found, even after a long search. In one case flagellation was still found after fifteen days, and in the other after thirteen days continuous administration of quinine in doses

CHART III.



of thirty grains daily (given by mouth in liquid form). In the first case it would appear that the flagellation was more delayed late on in the treatment than at the commencement. This may have been due to the fact that late in the treatment the crescents were becoming so scarce that it took a long time to find one, though I am inclined to suspect that it was due to the cold weather which set in at the time. In Liverpool, flagellation does not as a rule occur till about twenty minutes' exposure, but I note that in the many specimens sent to me by Dr. James from Panama that his crescents flagellated in ten minutes, and often as early as four minutes after exposure. This point, however, requires further observation.

It would appear to me, therefore, that the male crescents are quite as resistant to quinine as the female variety; and that no drug or other method, so far, has been found which can directly destroy crescents, that the only known method of destroying them is by indirect means, in other words, we can only destroy crescents by destroying the asexual parasites, which are the crescent producers. When these are destroyed the source of crescent supply is cut off, and the crescents remaining, live their natural term of life and die a natural death. This occurs within three weeks after the attack on the asexual forms, and, as the best agents for destroying the latter are quinine and methylene blue, hence these drugs are the best drugs for cleansing the system of crescents. I do not think it is to be greatly regretted that we have no specific drug for crescent destruction, because every case of malaria should have a prolonged course of thorough quinine treatment for at least a month to destroy the asexual parasites, and this length of treatment also destroys the crescents indirectly at the same time. I cannot see my way to believe that relapses are due to surviving crescents undergoing parthenogenesis. Relapses can be explained just as readily by the supposition that they are due to the successive sporulations and consequent increase of surviving asexual forms, for although in the vast majority of cases, quinine rapidly reduces the number of asexual parasites to below the detectable limit, yet all of them are not necessarily destroyed after a severe treatment. A case published by Ross and Thomson (1912) shows that the asexual parasites may show great resistance to quinine. Again,

though the occurrence of parthenogenesis in malaria is quite possible. yet it must indeed be very rare and unusual, as very few observers have seen it in crescents, at any rate.

(B) CONCLUSIONS REGARDING MALARIAL PROPHYLAXIS

There has always been a considerable controversy regarding the respective merits of mosquito destruction and quininisation of the population as a means of reducing the incidence of malaria. I think, as a general rule, the former method is the better, because, as Sir Ronald Ross has pointed out, mosquitos are pests causing much inconvenience quite apart from malaria, and they carry several other diseases, so that their destruction is desired for more than one reason. In some cases, however, the quinine method may be more practicable in places where the population is sparse and scattered, and where swamps abound, but there is no reason why both methods should not be carried out simultaneously, for in rendering a malarious locality healthy it is obvious that the two means of prevention complement each other and are better than one alone. The mosquito method alone, destroys one stage of the parasite with its host, and hence prevents the spread of the disease, but the human population already infected, remain so, often for months and sometimes for years. To relieve these, quinine must be given, and, if the amount given is adequate, not only are they relieved of their sickness, but their crescents are destroyed, so that another link in the perpetuation of the disease is broken. I think all are agreed on this point. But there still remains to be discussed, the question as to the best procedure, and best method of administration of quinine to a population to cleanse it of malaria. In the light of recent researches on the subject, I am going to bring forward ideal methods, which, though impossible to carry into practice, as stated, may yet serve as guides, so that those practical forces which are available, namely, money, legislature and medical staff, may be directed in the most profitable manner.

The Ideal Methods of Quinisation of a population, showing the demands of science necessary for the certain and rapid extinction of malaria by quinine alone.

In British colonies where malaria is rampant the ideal aim of experts is to get every person to take five grains of quinine daily, whether ill or not. Those who are ill with malaria, of course, would take more than this amount daily, till better, and then proceed as before. In carrying out this ideal, therefore, each adult would take 1,825 grains of quinine per annum, if well during the year, and more, say 2,000 grains per annum, if ill at some period of that year. Though this method is undoubtedly excellent, yet I think that the following method would be much more scientific and efficacious, and shall call it *Ideal Method A* :—‘That every adult person in the population (children in proportion according to age) should take twenty grains of quinine daily and simultaneously for a period of three weeks, quarterly, i.e., four times a year.’ This amounts to 1,680 grains per adult per annum, if well during the year, and probably 1,800 grains, if ill at some period in the year. This, in the aggregate, is less quinine than in the former method.

The faults of the 5 grains daily method :—

(1) Five grains of quinine daily is insufficient to prevent infection from mosquitos. I have known several cases of fever contracted during this daily dosage.

(2) Five grains of quinine daily will take a long time to eradicate malaria from the system. In many cases it will not eradicate it. The fact that a person can take an acute malarial attack during such dosage, proves that it is an insufficient amount to render the blood uninhabitable to the parasite.

(3) This amount of quinine makes the blood less suitable for the parasites, and, hence, tends to keep the disease latent in the system without properly curing it. A few parasites may be present in the blood not sufficient to cause fever, and the person may feel comparatively well and congratulate himself that he is free from the disease, yet he may be harbouring numerous crescents for long periods of time, since those latent chronic cases are often the most fertile producers of crescents (Thomson, 1911).

Points in favour of 'Ideal Method A.'

(1) The administration of quinine in doses of twenty grains daily for three weeks is almost certain to destroy both the asexual and sexual parasites.* After this period, the person will be non-infective to mosquitos, and, in the great majority of cases, will be cured of the disease. Very few patients have a tendency to relapse after this treatment. By this method, therefore, every person would be non-infective to mosquitos, and freed from a tendency to relapse, four times a year.

(2) Infective mosquitos must necessarily become much fewer in number.

(3) The amount of quinine taken is less in the end, and none is taken during nine months of the year.

(4) After the third day the majority of people feel very little inconvenience when taking 20 grains of quinine daily. I have satisfied myself on this point over and over again with regard to adult males, whilst in hospital and doing light indoor work.†

(5) It is quite as practicable a method as the five grain daily method. It would be as easy to make a population take 20 grains daily for 3 weeks, quarterly, as to make it take 5 grains daily for a year.

As an alternative to the above, I will now put forward '*Ideal Method B,*' which embodies the same scientific principles as 'A,' but which is more scientific and less tyrannical in its administration. This Method B differs from A in that a quarterly census of the blood of the population would be taken before administering the quarterly quinine. Only those who had parasites in their blood would require to take the 3 weeks' course, and those with crescents would, if possible, be isolated in mosquito-proof hospitals till non-infective. Further, immigrants would not be allowed to enter the area until their blood had been examined and pronounced non-infective. Infective immigrants would require the 3 weeks' period of treatment, with isolation, before being admitted to the population. With regard to the blood census, the quickest and surest method of examining the blood would be obtained by Ross's 'Thick Film Method' (James, 1911). The blood of several

* Exceptions to this occur. See Ross and Thomson (1912).

† It may not be so with those who have to do outdoor work during this treatment.



individuals could be placed on the same slide and numbered. This would reduce the number of slides required. No skill is required in smearing the blood, and as the blood by this method is concentrated about 20 times more than in ordinary smears, a two minutes' microscopic search is sufficient to decide the presence or absence of parasites. To carry out this blood census it would require one medical man with several assistants per 1,000 of the population, during the time of the census. It might be sufficient to make a blood census only of the children up to a certain age, and in places where malaria was not excessive, it might be sufficient to confine this method to those who were ill, especially with regard to children.

Before concluding I would like to state once more that the methods put forward above are ideal, and though they cannot be carried out to the letter in practice, yet they must form the ideal basis of malarial prevention by quinine, and they must, therefore, be considered in attempts to form systems of state medicine and sanitation in tropical countries, and it should be remembered that the carrying out of these methods in part only must always do some good. It is better to understand what is really required by science, and, looking at the great difficulties of giving an effectual quinine prophylaxis, a simultaneous though partial mosquito reduction will probably be always required.

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